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(71) Applicant *(for all designated States except US)*: FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : OKADA, Satoshi [JP/JP]; 13-1, Namiki 4-chome, Tsukuba-shi, Ibaraki 305 (JP). SAWADA, Kozo [JP/JP]; 1-602-301, Azuma, Tsukuba-shi, Ibaraki 305 (JP). KAYAKIRI, Natsuko [JP/JP]; 2-5-4-506, Umezono, Tsukuba-shi, Ibaraki 305 (JP). SAWADA, Yuki [JP/JP]; 1-602-208, Azuma, Tsukuba-shi, Ibaraki 305 (JP). TANAKA, Hirokazu [JP/JP]; 1-4-8, Ottominami, Tsuchiura-shi, Ibaraki 300 (JP). HASHIMOTO, Masashi [JP/JP]; 2-2-8-1205, Shinmachi, Toride-shi, Ibaraki 302 (JP).

(74) Agent: SEKI, Hideo; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).

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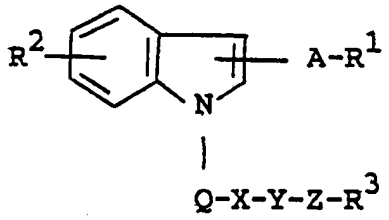
(54) Title: INDOLE DERIVATIVES



(I)

(57) Abstract

Indole derivatives of formula (I), or a salt thereof, which are useful as a testosteron 5α-reductase inhibitor.

DESCRIPTION

INDOLE DERIVATIVES

The present invention relates to novel indole derivatives and a pharmaceutically acceptable salt thereof. More particularly, it relates to novel indole derivatives and a pharmaceutically acceptable salt thereof which have pharmacological activities such as inhibitory activity on testosteron 5α-reductase and the like, to process for preparation thereof, to a pharmaceutical composition comprising the same and to a use of the same as a medicament.

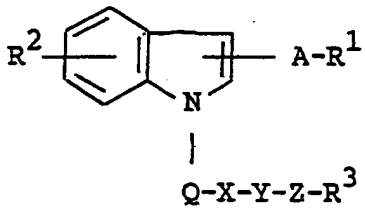
Accordingly, one object of the present invention is to provide novel indole derivatives and a pharmaceutically acceptable salt thereof, which are useful as a testosteron 5α-reductase inhibitor.

Another object of the present invention is to provide process for preparation of said indole derivatives or a salt thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said indole derivatives or a pharmaceutically acceptable salt thereof.

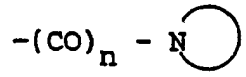
Still further object of the present invention is to provide a use of said indole derivatives or a pharmaceutically acceptable salt thereof as a medicament such as testosteron 5α-reductase inhibitor useful for treating or preventing testosteron 5α-reductase mediated diseases such as alopecia, acnes, prostatism, and the like in human being or animals.

The indole derivatives of the present invention are novel and can be represented by the formula (I) :

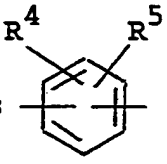
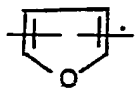


(I)

wherein R^1 is carboxy or protected carboxy,
R^2 is hydrogen, lower alkyl or halogen,
R^3 is aryl or ar(lower)alkyl, each of which may have suitable substituent(s), or a group of the formula :



in which  is heterocyclic group containing nitrogen atom, and
n is 0 or 1,
A is lower alkylene which may be substituted by oxo or lower alkenylene,
Q is carbonyl, sulfonyl or lower alkylene,

X is  or 

in which R^4 is hydrogen or lower alkyl, and
R^5 is hydrogen, lower alkyl or $Y\text{-}Z\text{-}R^3$,

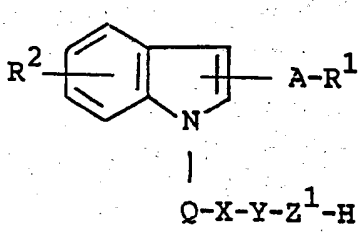
Y is bond or lower alkylene,

Z is bond, lower alkylene, lower alkenylene, -O-, $-S-$ or $-\overset{R^6}{\underset{|}{N}}-$,
in which R^6 is lower alkyl, ar(lower)alkyl which may have suitable substituent(s) or amino protective group; or

$X-Y-Z-R^3$ is 6H-dibenzo[b,d]pyranyl which may have suitable substituent(s).

According to the present invention, the object compound (I) and a salt thereof can be prepared by the following processes.

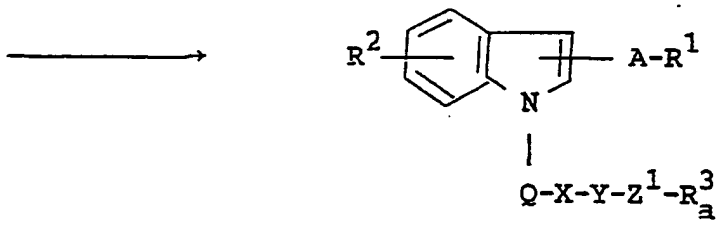
Process 1



(II)
or a salt thereof

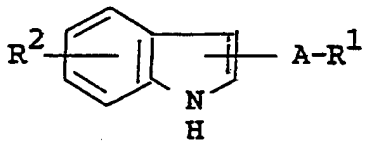
+ $W^1 - R^3_a$

(III)
or a salt thereof



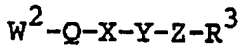
(I-a)
or a salt thereof

Process 2

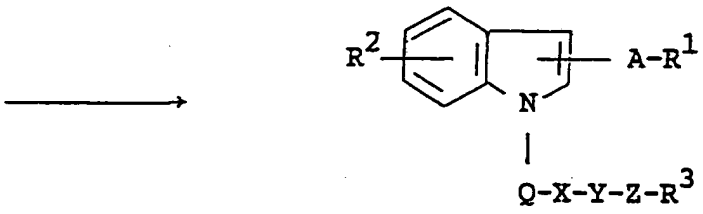


(IV)
or a salt thereof

+

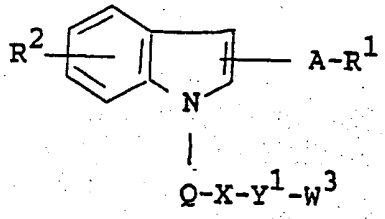


(V)
or a salt thereof



(I)
or a salt thereof

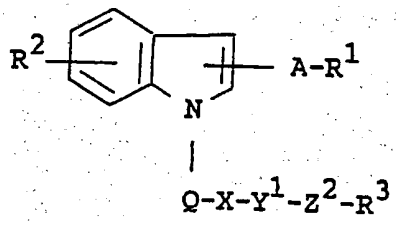
Process 3



(VI)
or a salt thereof

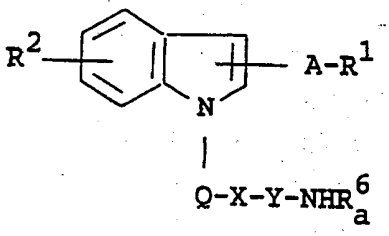
+ $H-Z^2-R^3$

(VII)
or a salt thereof



(I-b)
or a salt thereof

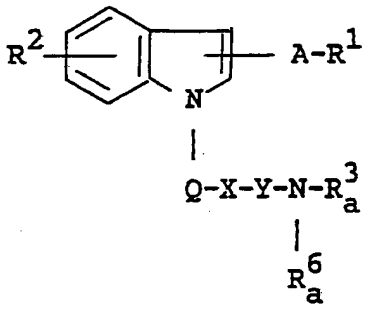
Process 4



(VIII)
or a salt thereof

+ $W^1 - R^3_a$

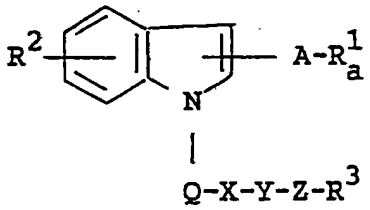
(III)
or a salt thereof



(I-c)

or a salt thereof

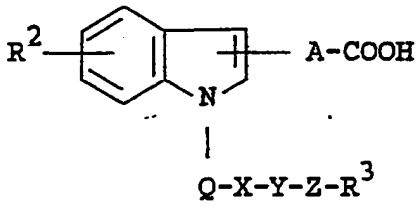
Process 5



Elimination of the carboxy protective group ⟶

(I-d)

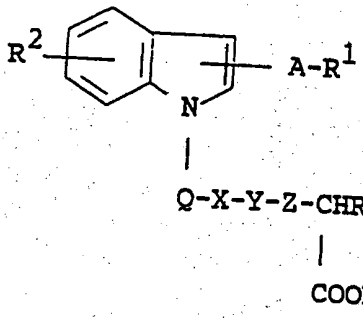
or a salt thereof



(I-e)

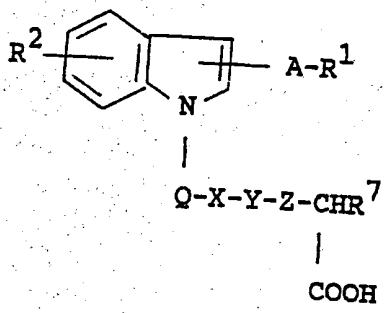
or a salt thereof

Process 6



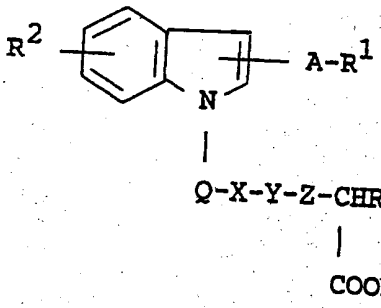
Elimination of the carboxy protective group

(I-f)
or a salt thereof



(I-g)
or a salt thereof

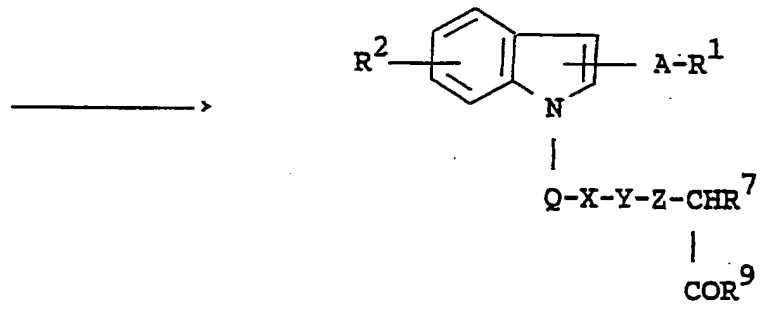
Process 7



+ H - R^9

(I-g)
or its reactive derivative at the carboxy group
or a salt thereof

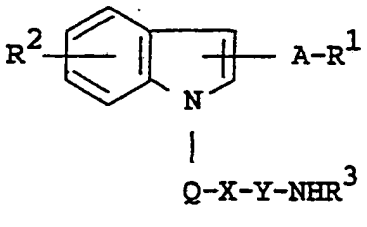
(VII)
or its reactive derivative at the amino group
or a salt thereof



(I-h)

or a salt thereof

Process 8



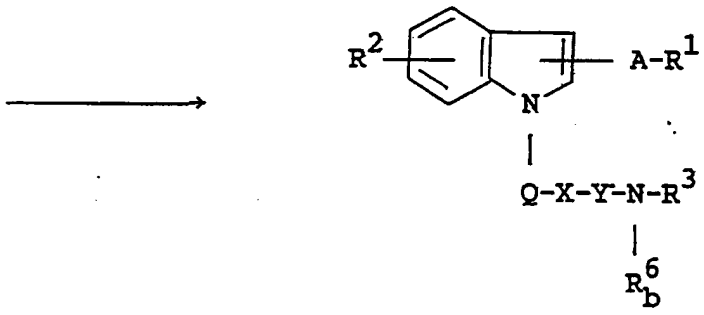
(X)

or a salt thereof

+ $W^4 - R_b^6$

(XI)

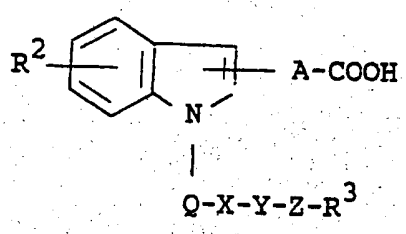
or a salt thereof



(I-i)

or a salt thereof

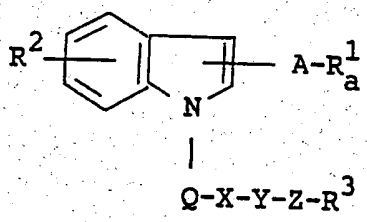
Process 9



Introduction of the carboxy protective group

(I-e)

or a salt thereof



(I-d)

or a salt thereof

wherein R^1, R^2, R^3, R^4, R^5, A, Q, X, Y and Z are each as defined above,

R^1_a is protected carboxy,

R^3_a is ar(lower)alkyl which may have suitable substituent(s) or a group of the formula :

$$-(CO)_n - N\bigcirc$$

in which $-N\bigcirc$ and n are each as defined above,

R^6_b is lower alkyl,

ar(lower)alkyl which may have suitable substituent(s) or amino protective group,

R^7 is aryl which may have suitable substituent(s),

R^8 is carboxy protective group,

R^9 is amino which may have suitable substituent(s),

W^1, W^2, W^3 and W^4 are each acid residue,

Y^1 is lower alkylene,

Z^1 is -O-, -S- or $-N(R^6_a)-$ in which R^6_a is lower alkyl or amino protective group, and

Z^2 is -O-, -S- or $-N(R^6)-$ in which R^6 is as defined above.

Suitable salts of the compounds (I) are conventional non-toxic, pharmaceutically acceptable salt and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt, cesium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), etc.; an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.); and the like, and the preferable example thereof is an acid addition salt.

With respect to the salt of the compounds (I-a) to

(I-i), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X) and (XI) in Processes 1 to 9, the suitable examples of the salts of these compounds are to be referred to those as exemplified for the object compound (I).

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, unless otherwise indicated.

Suitable "lower alkyl" may include straight or branched one, having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, and the like, preferably one having 1 to 4 carbon atoms.

The term "halogen" means fluoro, chloro, bromo and iodo.

Suitable "lower alkylene" means straight or branched bivalent lower alkane such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, propylene, and the like, which may be substituted by oxo.

Suitable "acid residue" may include halogen (e.g. fluoro, chloro, bromo, iodo), acyloxy (e.g. acetoxy, tosyloxy, mesyloxy, etc.), aryloxy (e.g. phenoxy, etc.) and the like.

Suitable "lower alkenylene" may include one having 2 to 6 carbon atoms such as vinylene, propenylene, and the like.

Suitable "aryl which may have suitable substituent(s)" may include a conventional group such as aryl (e.g. phenyl, naphthyl, etc.), substituted aryl, for example, lower alkylaryl (e.g. tolyl, xylyl, mesityl,

cumenyl, isobutylphenyl, isopentylphenyl, etc.), haloaryl (e.g. chlorophenyl, bromophenyl, dichlorophenyl, etc.), lower alkoxyaryl (e.g. isopropoxyphenyl, etc.), lower alkylcarbamoylaryl (e.g. t-butylcarbamoylphenyl, etc.), and the like.

Suitable "ar(lower)alkyl which may have suitable substituent(s)" may include a conventional group such as ar(lower)alkyl (e.g. trityl, benzhydryl, benzyl, phenethyl, naphthylmethyl, etc.), substituted ar(lower)alkyl, for example, ar(lower)alkyl substituted by one or more substituents such as lower alkyl as mentioned above, halogen as mentioned above, cyano, carboxy, protected carboxy as mentioned below, aryl which may have suitable substituent(s) as mentioned above, amidated carboxy as mentioned below and oxo. Specific examples of thus defined "ar(lower)alkyl which may have suitable substituents" may be methylbenzyl, propylbenzyl, isobutylbenzyl, methylphenylethyl, isobutylphenylethyl, methylphenylpropyl, isobutylphenylpropyl, methylphenylpentyl, isobutylphenylpentyl, bis(methylphenyl)methyl, bis(propylphenyl)methyl, bis(butylphenyl)methyl, bis(isobutylphenyl)methyl, bis(chlorophenyl)methyl, (cyano)(isobutylphenyl)methyl, (carboxy)(isobutylphenyl)methyl, (benzyloxycarbonyl)(isobutylphenyl)methyl, (N,N-diethylcarbamoyl)(isobutylphenyl)methyl, (t-butylcarbamoyl)(isobutylphenyl)methyl, (phenylcarbamoyl)(isobutylphenyl)methyl, (isobutylphenylcarbamoyl)(isobutylphenyl)methyl, etc.], benzoyl, isobutylbenzoyl, and the like.

Suitable "amino protective group" may be a conventional protective group, which is used in the field of organic chemistry, that is, may include acyl such as lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl,

etc.), lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl, etc.), and the like.

Suitable "protected carboxy" may include an esterified carboxy group.

Suitable examples of the ester moiety of an "esterified carboxy" may be the ones such as lower alkyl ester (e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, hexyl ester, 1-cyclopropylethyl ester, etc.) which may have at least one suitable substituent(s), for example, lower alkanoyloxy(lower)alkyl ester (e.g. acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 1(or 2)-acetoxyethyl ester, 1(or 2 or 3)-acetoxypropyl ester, 1(or 2 or 3 or 4)-acetoxybutyl ester, 1(or 2)-propionyloxyethyl ester, 1(or 2 or 3)-propionyloxypropyl ester, 1(or 2)-butyryloxyethyl ester, 1(or 2)-isobutyryloxyethyl ester, 1(or 2)-pivaloyloxyethyl ester, 1(or 2)-hexanoyloxyethyl ester, isobutyryloxymethyl ester, 2-ethylbutyryloxymethyl ester, 3,3-dimethylbutyryloxymethyl ester, 1(or 2)-pentanoyloxyethyl ester, etc.) lower alkanesulfonyl(lower)alkyl ester (e.g. 2-mesylethyl ester, etc.), mono(or di or tri)-halo(lower)alkyl ester (e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.), lower alkoxycarbonyloxy(lower)alkyl ester (e.g. methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, 2-methoxycarbonyloxyethyl ester, 1-ethoxycarbonyloxyethyl ester, 1-isopropoxycarbonyloxyethyl ester, etc.), phtahlidylidene(lower)alkyl ester, or (5-lower alkyl-2-oxo-1,3-dioxol-4-yl)(lower)alkyl ester (e.g. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester,

(5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, etc.; lower alkenyl ester (e.g. vinyl ester, allyl ester, etc.); lower alkynyl ester (e.g. ethynyl ester, propynyl ester, etc.); ar(lower)alkyl ester which may have at least one suitable substituent(s) (e.g. benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-tert-butylbenzyl ester, etc.); aryl ester which may have at least one suitable substituent(s) (e.g. phenyl ester, 4-chlorophenyl ester, tolyl ester, tert-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, etc.); phthalidyl ester; and the like.

Preferable examples of the esterified carboxy as mentioned above may include lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, tert-pentyloxycarbonyl, hexyloxycarbonyl, 1-cyclopropylethoxycarbonyl, etc.).

Suitable "carboxy protective group" may be the ester moiety of the above defined "protected carboxy" and may include lower alkyl (e.g. methyl, ethyl, etc.), ar(lower)alkyl (e.g. benzyl, etc.), and the like.

Suitable "amino which may have suitable substituent(s)" is conventional one used in a pharmaceutical field and may include amino, mono or di(lower)alkylamino (e.g. methylamino, dimethylamino, ethylamino, diethylamino, butylamino, t-butylamino, etc.), arylamino (e.g. phenylamino, etc.), lower alkylarylamino (e.g. isobutylphenylamino, etc.), and the like.

Suitable "heterocyclic group containing nitrogen atom" may include saturated or unsaturated monocyclic or

polycyclic heterocyclic group containing at least one nitrogen atom. Especially preferable heterocyclic group may be 5- or 6- membered aliphatic heteromonocyclic group (e.g. morpholinyl, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc.), unsaturated condensed heterocyclic group such as dibenzo[6 or 7-membered unsaturated]heteromonocyclic group (e.g. phenoxazinyl, phenothiazinyl, 10,11-dihydro-5H-dibenzoazepinyl, etc.), and the like.

Suitable "amidated carboxy" may carbamoyl which may have suitable substituent(s) and may include carbamoyl, mono or di(lower)alkylcarbamoyl (e.g. methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl diethylcarbamoyl, butylcarbamoyl, t-butylcarbamoyl, etc.), lower alkylaryl-carbamoyl (e.g. isobutylphenylcarbamoyl, etc.), and the like.

Suitable "6H-dibenzo[b,d]pyranyl which may have suitable substituent(s)" may include 6H-dibenzo[b,d]pyranyl substituted by lower alkyl as mentioned above (e.g. 8-isobutyl-3,4,6,6-tetramethyl-6H-dibenzo[b,d]pyranyl, etc.), and the like.

Particularly, the preferred embodiments of R^1, R^2, R^3, A, Q, X, Y and Z are as follows.

R^1 is carboxy;

lower alkoxycarbonyl, more preferably C_1-C_4 alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, etc.); or

ar(lower)alkoxycarbonyl, more preferably mono- or di- or triphenyl(C_1-C_4)alkoxycarbonyl (e.g. benzyloxycarbonyl, etc.),

R^2 is hydrogen;

lower alkyl, more preferably C_1-C_4 alkyl (e.g. methyl, etc.); or

halogen (e.g. chloro, etc.),

R^3 is aryl which may be substituted by one to three substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, halogen and lower alkylcarbamoyl more preferably phenyl which may be substituted by one to three substituent(s) selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and C_1-C_4 alkylcarbamoyl (e.g. phenyl, isobutylphenyl, isopentylphenyl, isopropoxyphenyl, bromophenyl, dichlorophenyl, t-butylcarbamoylphenyl, etc.);
ar(lower)alkyl which may be substituted by one to three substituents selected from the group consisting of lower alkyl, halogen, cyano, carboxy, protected carboxy, amidated carboxy, and oxo, more preferably mono- or di- or triphenyl(lower)alkyl which may be substituted by one or two the groups selected from lower alkyl, halogen, cyano, carboxy, phenyl(lower)-alkoxycarbonyl, mono or di(lower)alkylcarbamoyl, phenylcarbamoyl and lower alkylphenylcarbamoyl, most preferably mono- or di- or triphenyl(C_1-C_6)alkyl which may be substituted by the group selected from (C_1-C_4)alkyl, halogen, cyano, carboxy, phenyl(C_1-C_4)alkoxycarbonyl, mono or di(C_1-C_4)alkylcarbamoyl, phenylcarbamoyl, (C_1-C_4)alkylphenylcarbamoyl and oxo (e.g. benzyl, propylbenzyl, isobutylbenzyl, isobutylphenylethyl, isobutylphenylpropyl, isobutylphenylpentyl, bis(isobutylphenyl)methyl, dichlorobenzyl, bis(chlorophenyl)methyl, (cyano)(isobutylphenyl)methyl, (carboxy)(isobutylphenyl)methyl, (benzyloxycarbonyl)-(isobutylphenyl)methyl, (N,N-diethylcarbamoyl)-(isobutylphenyl)methyl, (t-butylcarbamoyl)-(isobutylphenyl)methyl, (phenylcarbamoyl)-(isobutylphenyl)methyl, (isobutylphenylcarbamoyl)-

(isobutylphenyl)methyl, benzoyl, isobutylbenzoyl, etc.);

5- or 6- membered aliphatic heteromonocycliccarbonyl (e.g. piperidylcarbonyl, etc.); or

unsaturated condensed heterocyclic group (e.g. phenoxazinyl, phenothiazinyl, 10,11-dihydro-5H-dibenzo[b,f]azepinyl, etc.),

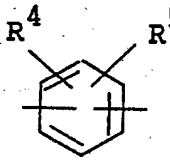
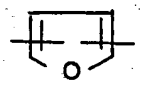
A is lower alkylene which may be substituted by oxo, more preferably C_1-C_4 alkylene which may be substituted by oxo (e.g. ethylene, trimethylene, oxotrimethylene, etc.); or

lower alkenylene, more preferably C_2-C_4 alkenylene (e.g. propenylene, etc.),

Q is carbonyl;

sulfonyl; or

lower alkylene, more preferably C_1-C_4 alkylene (e.g. methylene, etc.),

X is  or 

in which R^4 is hydrogen; or lower alkyl, more preferably C_1-C_4 alkyl (e.g. methyl, etc.),

R^5 is hydrogen; lower alkyl, more preferably C_1-C_4 alkyl (e.g. methyl, etc.); or ar(lower)alkylamino which may be substituted by the group(s) selected from lower alkyl or lower alkoxycarbonyl, more preferably C_1-C_4 alkylbenzylamino or N-C_1-C_4 alkoxycarbonyl-N-C_1-C_4 alkylbenzylamino (e.g. isobutylbenzylamino,

N-t-butoxycarbonyl-N-isobutylbenzylamino, etc.),

Y is bond; or

lower alkylene, more preferably C_1-C_4 alkylene (e.g. methylene, etc.), and

Z is bond;

lower alkylene, more preferably C_1-C_4 alkylene (e.g. methylene, etc.);

lower alkenylene, more preferably C_2-C_6 alkenylene (e.g. propenylene, etc.),

O ;

S; or

N-R^6

in which R^6 is lower alkyl, preferably C_1-C_4 alkyl (e.g. methyl, ethyl, etc.); lower alkoxycarbonyl, preferably C_1-C_4 alkoxycarbonyl (e.g. t-butoxycarbonyl, etc.);

ar(lower)alkyl which may be substituted by lower alkyl, more preferably mono- or di- or triphenyl(lower)alkyl which may be substituted by lower alkyl, most preferably mono- or di- or triphenyl(C_1-C_6)alkyl which may be substituted by C_1-C_4 alkyl (e.g. benzyl, isobutylbenzyl, etc.); or

X-Y-Z-R^3 is 6H-dibenzo[b,d]pyranyl which may be substituted by lower alkyl, more preferably 6H-dibenzo[b,d]pyranyl substituted by C_1-C_4 alkyl (e.g. 8-isobutyl-3,4,6,6-tetramethyl-6H-dibenzo[b,d]pyranyl, etc.).

The processes 1 to 9 for preparing the object compound (I) of the present invention are explained in detail in the following.

m), 2.30 (3H, d, J=0.4Hz), 2.50 (2H, d, J=7.5Hz), 6.90 (1H, s), 7.15-7.35 (5H, m), 7.40-7.55 (6H, m), 8.20 (2H, d, J=10Hz)

Preparation 52

A mixture of methyl 3-(chloroformyl)propionate (5.4 ml) and aluminum chloride (11.7 g) in dichloromethane was stirred at 25°C for 1 hour, and then a solution of 6-chloroindole (3.0 g) in dichloromethane (20 ml) at 25°C. The reaction mixture was stirred at 25°C for 1 hour, and poured into a mixture of ice and 1N hydrochloric acid. The organic layer was separated, washed with water, and dried over magnesium sulfate. After evaporation of the solvents the crystalline residue was recrystallized from ethyl acetate to give methyl 4-(6-chloroindol-3-yl)-4-oxobutyrate (2.54 g) as colorless crystals.

NMR ($CDCl_3$-CD_3OD, δ) : 2.80 (2H, t, J=7.5Hz), 3.19 (2H, t, J=7.5Hz), 3.70 (3H, s), 7.21 (1H, dd, J=2.5Hz, 8Hz), 7.39 (1H, d, J=2.5Hz), 7.85 (1H, s), 8.24 (1H, d, J=8Hz)

Preparation 53

1M solution of borane in tetrahydrofuran (4.6 ml) was added to a solution of methyl 4-(6-chloroindol-3-yl)-4-oxobutyrate (1.20 g) in tetrahydrofuran (40 ml) at 25°C over 5 minutes. The mixture was stirred at 25°C for 30 minutes, and 1M solution of borane in tetrahydrofuran 2.3 ml) was added at 25°C. The mixture was stirred at 25°C for 30 minutes, and then another 1M solution of borane in tetrahydrofuran (2.3 ml) was added at 25°C. The reaction mixture was stirred at 25°C for 15 minutes and poured into a mixture of ethyl acetate and 1N hydrochloric acid. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column

chromatography on silica gel (50 g) eluting with chloroform and by recrystallization from a mixture of ethyl acetate and hexane to give methyl 4-(6-chloroindol-3-yl)butyrate (669 mg) as pale yellow crystals.

NMR ($CDCl_3$, δ) : 1.92-2.15 (2H, m), 2.40 (2H, t, J=7.5Hz), 2.80 (2H, t, J=7.5Hz), 3.70 (3H, s), 7.00 (1H, d, J=2.5Hz), 7.10 (1H, dd, J=2.5Hz, 8Hz), 7.35 (1H, d, J=2.5Hz), 7.52 (1H, d, J=8Hz), 7.97 (1H, broad s)

Preparation 54

Methyl 4-(6-chloroindol-3-yl)butyrate (1.2 g) was hydrolyzed with 1N aqueous solution of sodium hydroxide (12 ml) and the crude product was recrystallized from a mixture of ethyl acetate and hexane to give 4-(6-chloroindol-3-yl)butyric acid (1.09 g) as colorless crystals.

NMR ($CDCl_3$-CD_3OD, δ) : 1.90-2.10 (2H, m), 2.38 (2H, t, J=7.5Hz), 2.79 (2H, t, J=7.5Hz), 6.98 (1H, s), 7.05 (1H, dd, J=2.5Hz, 8Hz), 7.35 (1H, d, J=2.5Hz), 7.50 (1H, d, J=8Hz)

Preparation 55

A solution of 3-indolebutyric acid (2.42 g) in N,N-dimethylformamide (20 ml) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 1.05 g) in N,N-dimethylformamide (30 ml) at 25°C over 15 minutes. The mixture was stirred at 25°C for 1.5 hours and cooled to -40°C. A solution of phenyl 3-(methoxymethoxy)benzoate (3.07 g) in tetrahydrofuran (40 ml) was added at -40°C over 30 minutes, and the mixture was stirred at the same temperature for 30 minutes. The mixture was worked up in an usual manner, and the crude product was purified by column chromatography on silica gel (50 g) eluting with chloroform and recrystallization from a mixture of ethyl

acetate and hexane to give 4-[1-[3-(methoxymethoxy)-benzoyl]indol-3-yl]butyric acid (2.96 g) as colorless crystals.

NMR ($CDCl_3$, δ) : 2.03 (2H, tt, J=6Hz, 6Hz), 2.42 (2H, t, J=6Hz), 2.66 (2H, t, J=6Hz), 3.50 (3H, s), 5.36 (2H, s), 7.10 (1H, s), 7.2-7.6 (7H, m), 8.40 (1H, d, J=8Hz)

Preparation 56

The following compound was obtained according to a similar manner to that of Preparation 55.

4-[1-[4-(Methoxymethoxy)benzoyl]indol-3-yl]butyric acid

NMR ($CDCl_3$, δ) : 2.05 (2H, m), 2.45 (2H, t, J=8Hz), 2.75 (2H, t, J=8Hz), 3.52 (3H, s), 5.25 (2H, s), 6.7-7.4 (5H, m), 7.55 (1H, m), 7.70 (2H, d, J=8Hz), 8.45 (1H, m)

Preparation 57

A mixture of 4-[1-[4-(methoxymethoxy)benzoyl]-indol-3-yl]butyrate (2.50 g), benzyl bromide (1.81 g) and potassium carbonate (2.82 g) in N,N-dimethylformamide (30 ml) was stirred at 25°C for 6 hours. The mixture was diluted with ethyl acetate, washed with 1N hydrochloric acid, water, aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated. The residue was chromatographed on silica gel (100 g) with dichloromethane to give benzyl 4-[1-[4-(methoxymethoxy)-benzoyl]indol-3-yl]butyrate (3.02 g) as a pale yellow oil.

NMR ($CDCl_3$, δ) : 2.05 (2H, m), 2.50 (2H, t, J=8Hz), 2.75 (2H, t, J=8Hz), 3.50 (3H, s), 5.10 (2H, s), 5.28 (2H, s), 7.1-7.2 (3H, m), 7.25-7.4 (7H, m), 7.55 (1H, m), 7.70 (2H, d, J=8Hz), 8.85 (1H, m)

Preparation 58

To a solution of 4-[1-[3-(methoxymethoxy)benzoyl]-indol-3-yl]butyric acid (1.4 g) in 1,4-dioxane (10 ml) was added 4N solution of hydrogen chloride in 1,4-dioxane (4 ml) at 25°C. The mixture was stirred at 25°C for 6 hours, and poured into a mixture of ether and 1N hydrochloric acid. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the crystalline residue was washed with isopropyl ether to give 4-[1-(3-hydroxybenzoyl)indol-3-yl]butyric acid (1.00 g) as colorless crystals.

NMR ($CDCl_3$-CD_3OD, δ) : 2.02 (2H, tt, J=6Hz, 6Hz), 2.40 (2H, t, J=6Hz), 2.75 (2H, t, J=6Hz), 7.05-7.2 (3H, m), 7.30-7.45 (4H, m), 7.6-7.7 (1H, m), 8.38 (1H, dd, J=2Hz, 8Hz)

Preparation 59

Benzyl 4-[1-[4-(methoxymethoxy)benzoyl]indol-3-yl]-butyrate (572 mg) was dissolved in trifluoroacetic acid (12 ml) at 25°C and the mixture was stirred at the same temperature for 15 minutes. After evaporation of the solvent, the residue was dissolved with ethyl acetate, washed with aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated. The residue was chromatographed on silica gel (30 g) eluting with a mixture of hexane and ethyl acetate (2:1) to give benzyl 4-[1-(4-hydroxybenzoyl)indol-3-yl]butyrate (350 mg) as a yellow oil.

NMR ($CDCl_3$, δ) : 2.10 (2H, m), 2.50 (2H, t, J=8Hz), 2.80 (2H, t, J=8Hz), 5.15 (2H, s), 6.98 (2H, d, J=10Hz), 7.2-7.6 (7H, m), 7.60 (1H, m), 7.65 (2H, d, J=10Hz), 8.40 (1H, m)

Example 1

A solution of 4-(indol-3-yl)butyric acid (1.25 g) in N,N-dimethylformamide (10 ml) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 541 mg) in N,N-dimethylformamide (20 ml) at 25°C over 15 minutes. The mixture was stirred at 25°C for 1 hour, and then a solution of phenyl 3-(3-isobutylphenoxymethyl)benzoate (2.22 g) in tetrahydrofuran (10 ml) was added at -40°C. The reaction mixture was stirred at -40°C for 30 minutes and poured into a mixture of ether and 1N hydrochloric acid. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. The residue was purified by column chromatography on silica gel (40 g) eluting with chloroform and by recrystallization from a mixture of ethyl acetate and hexane to give 4-[1-[3-(3-isobutylphenoxymethyl)benzoyl]indol-3-yl]butyric acid (1.45 g) as colorless crystals.

mp : 81-83°C

NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=4Hz), 1.88 (1H, m), 2.06 (2H, quintet, J=4Hz), 2.45 (2H, t, J=4Hz), 2.47 (2H, d, J=4Hz), 2.76 (2H, t, J=4Hz), 5.16 (2H, s), 6.75-6.87 (3H, m), 7.09 (1H, s), 7.20-7.77 (7H, m), 7.83 (1H, s), 8.40 (1H, dd, J=1Hz, 4Hz)

Example 2

The following compounds were obtained according to a similar manner to that of Example 1.

(1) 4-[1-[3-(4-Isopentylphenoxymethyl)benzoyl]indol-3-yl]butyric acid

mp : 114-116°C

NMR ($CDCl_3$, δ) : 0.92 (6H, d, J=4Hz), 1.4-1.7 (3H, m), 2.01 (2H, m), 2.42 (2H, t, J=4Hz), 2.54 (2H, dd, J=4Hz, 5Hz), 2.72 (2H, t, J=4Hz), 5.10 (2H,

s), 6.90 (2H, d, J=5Hz), 7.05-7.70 (9H, m), 7.80 (1H, t, J=1Hz), 8.38 (1H, dd, J=1Hz, 5Hz)

(2) 4-[1-[4-(4-Isobutylbenzyloxy)benzoyl]indol-3-yl]-butyric acid
mp : 156°C
NMR ($CDCl_3$, δ) : 0.95 (6H, d, J=7.5Hz), 1.8-2.2 (3H, m), 2.4-2.6 (4H, m), 2.78 (2H, t, J=7.5Hz), 5.15 (2H, s), 7.12 (2H, d, J=10Hz), 7.2-7.5 (7H, m), 7.60 (1H, m), 7.75 (2H, d, J=10Hz), 8.35 (1H, m)

(3) 4-[1-[3-[Bis(4-isobutylbenzyl)amino]benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.92 (12H, d, J=7.5Hz), 1.65-2.0 (2H, m), 2.0-2.1 (2H, m), 2.42 (2H, t, J=7.5Hz), 2.48 (4H, d, J=7.5Hz), 2.70 (2H, t, J=7.5Hz), 4.70 (4H, s), 6.9-7.1 (2H, m), 7.1-7.2 (8H, m), 7.25-7.5 (5H, m), 7.5-7.6 (1H, m), 8.40 (1H, d, J=7.5Hz)

(4) 4-[1-[2,3-Dimethyl-4-[1-(4-isobutylphenyl)ethoxy]-benzoyl]indol-3-yl]butyric acid
mp : 98-99°C
NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=7Hz), 1.67 (3H, d, J=6Hz), 1.85 (1H, m), 1.97 (2H, m), 2.22 (3H, s), 2.31 (3H, s), 2.3-2.5 (5H, m), 2.69 (2H, t, J=7.5Hz), 5.36 (1H, q, J=6Hz), 6.66 (1H, d, J=9Hz), 6.86 (1H, s), 7.04 (1H, d, J=9Hz), 7.11 (2H, d, J=8Hz), 7.2-7.4 (4H, m), 7.5-7.6 (1H, m), 8.23 (1H, d, J=7.5Hz)

(5) 4-[1-[3-[1-(4-Isobutylphenyl)ethoxy]benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.87 (6H, d, J=4Hz), 1.64 (3H, d, J=4Hz), 1.80 (1H, m), 1.98 (2H, quintet, J=4Hz),

2.40 (2H, t, J=4Hz), 2.41 (2H, d, J=4Hz), 2.72 (2H, t, J=4Hz), 5.32 (1H, q, J=4Hz), 6.8-7.4 (11H, m), 7.53 (1H, dd, J=2Hz, 5Hz), 8.35 (1H, dd, J=2Hz, 5Hz)

(6) 4-[1-[4,5-Dimethyl-3-[1-(4-isobutylphenyl)ethoxy]-benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=7.5Hz), 1.62 (3H, d, J=7.5Hz), 1.68-2.08 (3H, m), 2.22-2.49 (10H, m), 2.58-2.80 (2H, m), 6.78-6.88 (1H, m), 6.92-7.02 (2H, m), 7.02-7.16 (3H, m), 7.20-7.40 (3H, m), 7.48-7.60 (1H, m), 8.28-8.38 (1H, m)

(7) 4-[1-[3-(3,4-Dichlorophenoxymethyl)benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 1.90-2.10 (2H, m), 2.40 (2H, t, J=7.5Hz), 2.73 (2H, t, J=7.5Hz), 5.14 (2H, s), 6.84 (1H, dd, J=2.5Hz, 10Hz), 7.05 (1H, s), 7.09 (1H, d, J=2.5Hz), 7.20-7.45 (3H, m), 7.50-7.75 (4H, m), 7.78 (1H, s), 8.38 (1H, d, J=8Hz)

(8) 4-[1-[3-[Bis(4-isobutylphenyl)methylthio]benzoyl]-indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.85 (12H, d, J=6Hz), 1.80 (2H, m), 2.02 (2H, m), 2.36-2.50 (4H, m), 2.72 (2H, t, J=6Hz), 5.55 (1H, s), 6.95 (1H, s), 7.05 (4H, d, J=8Hz), 7.2-7.5 (9H, m), 7.5-7.6 (2H, m), 8.26 (1H, d, J=8Hz)

(9) 4-[5-Chloro-1-[3-(3-isobutylphenoxymethyl)benzoyl]-indol-3-yl]butyric acid
mp : 96-97°C
NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=7.5Hz), 1.70-2.10 (3H, m), 2.30-2.50 (4H, m), 2.69 (2H, t, J=7.5Hz), 5.10 (2H, s), 6.70-6.85 (3H, m), 7.10

(1H, s), 7.20 (1H, t, J=8Hz), 7.32 (1H, dd, J=2.5Hz, 8Hz), 7.45-7.75 (4H, m), 7.80 (1H, s), 8.30 (1H, d, J=8Hz)

(10) 4-[6-Chloro-1-[3-(3-isobutylphenoxymethyl)benzoyl]-indol-3-yl]butyric acid
mp : 126-127°C
NMR ($CDCl_3$, δ) : 0.89 (6H, d, J=7.5Hz), 1.72-2.10 (3H, m), 2.35-2.50 (4H, m), 2.70 (2H, t, J=9.5Hz), 5.5 (2H, s), 6.70-6.85 (3H, m), 7.05 (1H, s), 7.12-7.38 (2H, m), 7.40-7.75 (4H, m), 7.80 (1H, s), 8.49 (1H, d, J=2.5Hz)

(11) 4-[1-[3-(3,4-Dichlorobenzyloxy)benzoyl]indol-3-yl]-butyric acid
NMR ($CDCl_3$, δ) : 1.90-2.15 (2H, m), 2.41 (2H, t, J=7.5Hz), 2.71 (2H, t, J=7.5Hz), 5.02 (2H, s), 7.02 (1H, s), 7.12-7.65 (10H, m), 8.35 (1H, d, J=8Hz)

(12) 4-[1-[3-(3-Bromophenoxymethyl)benzoyl]indol-3-yl]-butyric acid
NMR ($CDCl_3$, δ) : 1.85-2.15 (2H, m), 2.42 (2H, t, J=7.5Hz), 2.70 (2H, t, J=7.5Hz), 5.10 (2H, s), 6.83-6.95 (1H, m), 7.00-7.20 (4H, m), 7.20-7.50 (2H, m), 7.50-7.75 (4H, m), 7.80 (1H, broad s), 8.38 (1H, d, J=8Hz)

(13) 4-[1-[3-[3-(Isopropoxy)phenoxymethyl]benzoyl]-indol-3-yl]butyric acid
mp : 80-82°C
NMR ($CDCl_3$, δ) : 1.33 (6H, d, J=7.5Hz), 1.90-2.13 (2H, m), 2.42 (2H, t, J=7.5Hz), 2.75 (2H, t, J=7.5Hz), 4.40-4.62 (1H, m), 5.11 (2H, s), 6.45-6.60 (3H, m), 7.08 (1H, s), 7.10-7.25 (1H,

m), 7.28-7.48 (2H, m), 7.48-7.63 (2H, m), 7.63-7.74 (2H, m), 7.81 (1H, broad s), 8.38 (1H, m)

(14) 4-[1-[3-[2-(4-Isobutylphenyl)-1-propenyl]benzoyl]-indol-3-yl]butyric acid
mp : 109-110°C
NMR ($CDCl_3$, δ) : 0.92 (6H, 7H), 1.87 (1H, m), 2.02 (2H, m), 2.30 (3H, d, J=1Hz), 2.4-2.6 (4H, m), 2.76 (2H, t, J=7.5Hz), 6.87 (1H, d, J=1Hz), 7.1-7.2 (3H, m), 7.3-7.6 (8H, m), 7.70 (1H, s), 8.40 (1H, m)

(15) 4-[1-[8-Isobutyl-3,4,6,6-tetramethyl-6H-dibenzo[b,d]-pyran-2-ylcarbonyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.95 (3H, d, J=7Hz), 1.70 (6H, s), 1.90 (1H, m), 2.03 (2H, m), 2.44 (2H, t, J=7.5Hz), 2.52 (2H, d, J=7Hz), 2.74 (2H, t, J=7.5Hz), 7.0-7.2 (3H, m), 7.2-7.5 (2H, m), 7.5-7.7 (3H, m), 8.33 (1H, m)

(16) 4-[1-[3-[2,2-Bis(4-isobutylphenyl)ethyl]benzoyl]-indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.80 (12H, d, J=7Hz), 1.75 (2H, m), 2.01 (2H, m), 2.3-2.5 (2H, m), 2.36 (4H, d, J=7Hz), 2.73 (2H, t, J=7.5Hz), 3.39 (2H, d, J=7.5Hz), 4.16 (1H, t, J=7.5Hz), 7.0-7.4 (6H, m), 7.00 (4H, d, J=8Hz), 7.10 (4H, d, J=8Hz), 7.4-7.5 (1H, m), 7.55 (1H, m), 8.25 (1H, m)

(17) 4-[1-[4-[2,2-Bis(4-isobutylphenyl)ethyl]benzoyl]-indol-3-yl]butyric acid
mp : 152°C
NMR ($CDCl_3$, δ) : 0.87 (12H, d, J=7Hz), 1.82 (2H, m),

1.9-2.1 (2H, m), 2.3-2.5 (2H, m), 2.42 (4H, d, J=7Hz), 2.74 (2H, t, J=7.5Hz), 3.42 (2H, d, J=7.5Hz), 4.20 (1H, t, J=7.5Hz), 7.0-7.2 (1H, m), 7.03 (4H, d, J=8Hz), 7.12 (4H, d, J=8Hz), 7.2-7.4 (2H, m), 7.5-7.6 (1H, m), 7.10 (2H, d, J=8Hz), 7.52 (2H, d, J=8Hz), 8.28 (1H, m)

(18) 4-[1-[4-(4-Isobutylphenoxy)benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.93 (6H, d, J=7Hz), 1.87 (1H, m), 2.04 (2H, quint, J=7.5Hz), 2.4-2.6 (4H, m), 2.76 (2H, t, J=7.5Hz), 7.01 (2H, d, J=8Hz), 7.05 (2H, d, J=8Hz), 7.16 (1H, s), 7.18 (2H, d, J=8Hz), 7.2-7.5 (2H, m), 7.57 (1H, d, J=7.5Hz), 7.71 (2H, d, J=8Hz), 8.35 (1H, d, J=7.5Hz)

(19) 4-[1-[4-(4'-Benzyloxycarbonyl)biphenylcarbonyl]-indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 2.03 (2H, m), 2.43 (2H, t, J=7.5Hz), 2.75 (2H, t, J=7.5Hz), 5.41 (2H, s), 7.13 (1H, s), 7.2-7.5 (7H, m), 7.58 (1H, d, J=7.5Hz), 7.72 (2H, d, J=8Hz), 7.76 (2H, d, J=8Hz), 7.83 (2H, d, J=8Hz), 8.18 (2H, d, J=8Hz), 8.41 (1H, d, J=7.5Hz)

(20) 4-[1-[3-[N-(4-Isobutylbenzoyl)-N-methylamino]-benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.81 (6H, d, J=6Hz), 1.7-1.9 (1H, m), 2.00 (2H, t, J=7Hz), 2.3-2.5 (4H, m), 2.71 (2H, t, J=7Hz), 3.52 (3H, s), 6.8-7.1 (4H, m), 7.2-7.6 (8H, m), 8.29 (1H, m)

(21) 4-[1-[3-[N-(4-Isobutylbenzyl)-N-(4-isobutylphenyl)-carbamoyl]benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.78 (6H, d, J=7Hz), 0.86 (6H, d,

J=7Hz), 1.6-1.9 (2H, m), 2.06 (2H, quint, J=7Hz), 2.3-2.5 (6H, m), 2.80 (2H, t, J=7Hz), 5.08 (2H, s), 6.76 (2H, d, J=8Hz), 6.91 (2H, d, J=8Hz), 6.94 (1H, s), 7.04 (2H, d, J=8Hz), 7.16 (2H, d, J=8Hz), 7.1-7.5 (4H, m), 7.5-7.7 (2H, m), 7.84 (1H, br s), 8.37 (1H, d, J=7.5Hz)

(22) 4-[1-[3-[N-(4-Isobutylbenzoyl)-N-(4-isobutylphenyl)-aminomethyl]benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.80 (12H, d, J=7Hz), 1.75 (2H, m), 2.05 (2H, quint, J=7Hz), 2.38 (4H, d, J=7Hz), 2.43 (2H, t, J=7.5Hz), 2.77 (2H, t, J=7Hz), 5.23 (2H, s), 6.83 (2H, d, J=8Hz), 6.90 (2H, d, J=8Hz), 6.94 (2H, d, J=8Hz), 7.11 (1H, s), 7.20 (2H, d, J=8Hz), 7.3-7.5 (4H, m), 7.59 (1H, d, J=7.5Hz), 7.6-7.8 (1H, m), 7.77 (1H, br s), 8.45 (1H, d, J=7.5Hz)

(23) 4-[1-[3-[N-(4-Isobutylbenzoyl)-(3-isobutylphenyl)-aminomethyl]benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.64 (6H, d, J=7Hz), 0.80 (6H, d, J=7Hz), 1.51 (1H, m), 1.74 (1H, m), 2.25 (2H, d, J=7Hz), 2.33 (2H, d, J=7Hz), 2.42 (2H, t, J=7Hz), 2.74 (2H, t, J=7Hz), 5.21 (2H, s), 6.59 (1H, br s), 6.8-7.0 (4H, m), 7.0-7.3 (4H, m), 7.5-7.3 (4H, m), 7.57 (1H, d, J=7.5Hz), 7.6-7.8 (1H, m), 7.75 (1H, br s), 8.42 (1H, d, J=7.5Hz)

(24) 4-[1-[3-[N-(4-Isobutylbenzyl)-N-(4-isobutylphenyl)-aminomethyl]benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.86 (6H, d, J=7Hz), 0.88 (6H, d, J=7Hz), 1.78 (2H, m), 1.98 (2H, quint, J=7.5Hz), 2.3-2.5 (6H, m), 2.70 (2H, t, J=7.5Hz), 4.6-4.7 (4H, m), 6.70 (1H, br s), 6.8-7.7 (15H, m), 8.35 (1H, d, J=7.5Hz)

(25) 4-[1-[3-[N-Benzoyl-N-(4-isobutylphenyl)aminomethyl]-benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.78 (6H, d, J=7Hz), 1.74 (1H, m), 2.35 (2H, d, J=7Hz), 5.21 (2H, s), 6.83 (2H, d, J=8Hz), 6.92 (2H, d, J=8Hz), 7.1-7.6 (11H, m), 7.68 (1H, d, J=7.5Hz), 8.0-8.2 (2H, m)

(26) 4-[1-[3-(4-Isobutylphenoxymethyl)benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.89 (6H, d, J=7Hz), 1.70-1.92 (1H, m), 1.95-2.12 (2H, m), 2.36-2.50 (4H, m), 2.75 (2H, t), 5.12 (2H, s), 6.88 (2H, d, J=8Hz), 7.07 (2H, d, J=8Hz), 7.08 (1H, s), 7.20-7.72 (6H, m), 7.80 (1H, s), 8.38 (1H, dd, J=1Hz, 8Hz)

(27) 4-[1-[4-(4-Propylbenzyloxy)benzoyl]indol-3-yl]-butyric acid
mp : 93-94°C
NMR ($CDCl_3$, δ) : 0.92 (3H, t, J=7.5Hz), 1.52-1.72 (2H, m), 1.95-2.22 (2H, m), 2.43 (2H, t, J=7.5Hz), 2.55 (2H, t, J=7.5Hz), 2.76 (2H, t, J=7.5Hz), 5.15 (2H, s), 6.92 (2H, d, J=8Hz), 7.08 (1H, s), 7.12 (2H, d, J=8Hz), 7.30-7.62 (5H, m), 7.75 (2H, d, J=8Hz), 8.38 (1H, dd, J=1Hz, 8Hz)

(28) 4-[1-[2,3-Dimethyl-5-(3-isobutylphenoxymethyl]-benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=7.5Hz), 1.75-2.10 (3H, m), 2.23 (3H, s), 2.38 (3H, s), 2.43-2.52 (4H, m), 2.72 (2H, t, J=7.5Hz), 5.07 (2H, s), 6.75-6.90 (4H, m), 7.20 (1H, dd, J=6Hz, 8Hz), 7.30-7.50 (5H, m), 7.58 (1H, dd, J=1Hz, 8Hz)

(29) 4-[1-[2,3-Dimethyl-5-(4-isobutylphenoxymethyl)-

benzoyl]indol-3-yl]butyric acid
NRM ($CDCl_3$, δ) : 0.90 (6H, d, J=7.5Hz), 1.7-2.1 (3H, m), 2.24 (3H, s), 2.40 (3H, s), 2.41-2.48 (4H, m), 2.72 (2H, t, J=7.5Hz), 5.06 (2H, s), 6.84 (1H, broad s), 6.90 (2H, d, J=8Hz), 7.08 (2H, d, J=8Hz), 7.28-7.46 (5H, m), 7.48 (1H, dd, J=1Hz, 8Hz)

(30) 4-[1-[3-(2-Isobutylphenoxymethyl)benzoyl]indol-3-yl]-butyric acid
NMR ($CDCl_3$, δ) : 0.89 (6H, d, J=7.5Hz), 1.81-2.15 (3H, m), 2.44 (2H, t, J=7.5Hz), 2.58 (2H, d, J=7.5Hz), 2.75 (2H, t, J=7.5Hz), 5.18 (2H, s), 6.83-7.02 (2H, m), 7.02-7.25 (3H, m), 7.25-7.50 (2H, m), 7.50-7.90 (5H, m), 8.40 (1H, m)

(31) 4-[1-[4-(4-Isobutylphenyl)benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.92 (6H, d, J=7.5Hz), 1.78-2.14 (4H, m), 2.42 (2H, t, J=7.5Hz), 2.54 (2H, d, J=7.5Hz), 2.76 (2H, t, J=7.5Hz) 7.17 (1H, s), 7.20-7.45 (4H, m), 7.58 (3H, d, J=8Hz), 7.77 (4H, A_2B_2, J=8Hz), 8.40 (1H, d, J=8Hz)

(32) 4-[1-[3-[2-(4-Isobutylphenyl)vinyl]benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=7.5Hz), 1.88 (1H, m), 2.01 (2H, m), 2.35-2.50 (4H, m), 2.75 (2H, t, J=7.5Hz), 7.0-7.6 (12H, m), 7.77 (1H, m), 7.87 (1H, m), 8.40 (1H, m)

(33) 4-[1-[4-[2-(4-Isobutylphenyl)-1-propenyl]benzoyl]-indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=0.75Hz), 1.90 (1H, m), 2.02 (2H, m), 2.35 (3H, t, J=0.5Hz),

2.45-2.55 (4H, m), 2.75 (2H, t, J=5Hz), 6.88 (1H, s), 7.12-7.20 (3H, m), 7.30-7.60 (7H, m), 7.75 (2H, d, J=7.5Hz), 8.40 (1H, m)

Example 3

A solution of 4-[1-(3-hydroxybenzoyl)indol-3-yl]-butyric acid (480 mg) in N,N-dimethylformamide (10 ml) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 131 mg) in N,N-dimethylformamide at 25°C over 15 minutes. The mixture was stirred at 25°C for 30 minutes, and then a solution of bis(4-isobutylphenyl)-bromomethane (640 mg) in tetrahydrofuran (10 ml) was added at 25°C. The reaction mixture was stirred at 25°C for 4 hours and allowed to stand at 25°C for 2 days. The mixture was worked up in an usual manner and the crude product was purified by column chromatography on silica gel (40 g) eluting with chloroform to give 4-[1-[3-[bis-(4-isobutylphenyl)methoxy]benzoyl]indol-3-yl]butyric acid (0.37 g) as a colorless oil.

NMR ($CDCl_3$, δ) : 0.88 (12H, d, J=6Hz), 1.86 (2H, m), 2.02 (2H, m), 2.37-2.50 (4H, m), 2.62 (2H, t, J=6Hz), 6.23 (1H, s), 7.00 (1H, s), 7.10 (4H, d, J=8Hz), 7.15-7.40 (10H, m), 7.58 (1H, m), 8.47 (1H, dd, J=2Hz, 8Hz)

Example 4

The following compounds were obtained according to a similar manner to that of Example 3.

(1) Benzyl 4-[1-[4-[bis(4-isobutylphenyl)methoxy]-benzoyl]indol-3-yl]butyrate

NMR ($CDCl_3$, δ) : 0.90 (12H, d, J=5Hz), 1.85 (2H, m), 2.05 (2H, m), 2.35-2.80 (6H, m), 2.70 (2H, t, J=8Hz), 5.10 (2H, s), 6.28 (1H, s), 7.00-7.40 (18H, m), 7.50 (1H, m), 7.65 (1H, m), 8.30 (1H, m)

(2) Benzyl 4-[1-[4-[1-(4-isobutylphenyl)ethoxy]benzoyl]-indol-3-yl]butyrate

NMR ($CDCl_3$, δ) : 0.85 (6H, d, J=5Hz), 1.62 (3H, d, J=7Hz), 1.80 (1H, m), 2.00 (2H, m), 2.8-2.95 (4H, m), 2.65 (2H, t, J=8Hz), 5.02 (2H, s), 5.32 (1H, q, J=7Hz), 6.90 (2H, d, J=10Hz), 7.00-7.10 (3H, m), 7.15-7.45 (9H, m), 7.42 (1H, m), 7.55 (2H, d, J=10Hz), 8.23 (1H, m)

Example 5

A mixture of benzyl 4-[1-[4-[bis(4-isobutylphenyl)-methoxy]benzoyl]indol-3-yl]butyrate (500 mg) and 10% palladium on activated carbon (50 mg) in 1,4-dioxane (10 ml) was stirred under hydrogen atmosphere (1 atm) at 25°C for 8 hours. The catalyst was filtered off and the filtrate was evaporated. The residue was treated with isopropyl ether and the solid was filtered to give 4-[1-[4-[bis(4-isobutylphenyl)methoxy]benzoyl]indol-3-yl]butyric acid (162 mg) as white powder.

NMR ($CDCl_3$, δ) : 0.90 (12H, d, J=5Hz), 1.80 (2H, m), 2.05 (2H, m), 2.35-2.50 (6H, m), 2.72 (2H, t, J=8Hz), 6.25 (1H, s), 7.00-7.20 (7H, m), 7.25-7.40 (6H, m), 7.55 (1H, m), 7.65 (2H, d, J=10Hz), 8.30 (1H, m)

Example 6

The following compound was obtained according to a similar manner to that of Example 5.

4-[1-[4-[1-(4-Isobutylphenyl)ethoxy]benzoyl]-indol-3-yl]butyric acid

NMR ($CDCl_3$, δ) : 0.85 (6H, d, J=6Hz), 1.65 (3H, d, J=7Hz), 1.85 (1H, m), 2.00 (2H, m), 2.35-2.50 (4H, m), 2.72 (2H, t, J=8Hz), 5.40 (1H, q, J=7Hz), 6.95 (2H, d, J=10Hz), 7.05-7.20 (3H, m),

7.20-7.40 (4H, m), 7.50-7.70 (3H, m), 8.30 (1H, m)

Example 7

4N-Hydrogen chloride in 1,4-dioxane (1 ml) was added to a solution of methoxymethyl 4-[1-[4-(4'-tert-butylcarbamoyl)biphenylcarbonyl]indol-3-yl]butyrate (30 mg) in 1,4-dioxane (0.5 ml). The mixture was stirred at room temperature for 20 minutes and partitioned between ethyl acetate and water. The organic layer was washed with water, dried over magnesium sulfate and evaporated. The residue was washed with diisopropyl ether to give 4-[1-[4-(4'-tert-butylcarbamoyl)biphenylcarbonyl]indol-3-yl]butyric acid as a white powder (12.1 mg).

mp : 174-175°C

NMR ($CDCl_3$, δ) : 1.51 (9H, s), 2.03 (2H, m), 2.44 (2H, t, J=7.5Hz), 2.76 (2H, t, J=7.5Hz), 6.04 (1H, br s), 7.14 (1H, s), 7.3-7.5 (2H, m), 7.59 (1H, d, J=7.5Hz), 7.6-7.9 (8H, m), 8.41 (1H, d, J=7.5Hz)

Example 8

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (30 mg) and 1-hydroxybenzotriazole (20 mg) was added to a mixture of methoxymethyl 4-[1-[4-(4'-carboxy)biphenylcarbonyl]indol-3-yl]butyrate (40 mg) and tert-butylamine (15 mg) in dichloromethane (3 ml). The mixture was stirred at room temperature for 5 hours and poured into ice water. The organic layer was washed with water, dried over magnesium sulfate and evaporated. The residue was purified by thin-layer chromatography on silica gel using a mixture of n-hexane and ethyl acetate (1:1) as the eluent. Appropriate fractions were combined, extracted with ethyl acetate and evaporated to give methoxymethyl 4-[1-[4-[4'-tert-butylcarbamoyl)biphenyl-

carbonyl]indol-3-yl]butyrate (26 mg) as a colorless foam.

NMR ($CDCl_3$, δ) : 1.52 (9H, s), 2.05 (2H, m), 2.45 (2H, t, J=7.5Hz), 2.76 (2H, t, J=7.5Hz), 3.44 (3H, s), 5.21 (2H, s), 6.02 (1H, br s), 7.15 (1H, s), 7.3-7.5 (2H, m), 7.61 (1H, d, J=7.5Hz), 7.3-7.4 (8H, m), 8.42 (1H, d, J=7.5Hz)

Example 9

A mixture of methoxymethyl 4-[1-[4-(4'-benzyloxycarbonyl)biphenylcarbonyl]indol-3-yl]butyrate (0.70 g) and 10% palladium on carbon (0.26 g) in ethyl acetate (30 ml) was shaken under hydrogen atmosphere (3.5 atm) at room temperature for 2 hours. The catalyst was filtered off and the filtrate was evaporated. The residue was washed with diisopropyl ether to give methoxymethyl 4-[1-[4-(4'-carboxy)biphenylcarbonyl]indol-3-yl]butyrate (0.21 g) as a white powder.

mp : 188-189°C

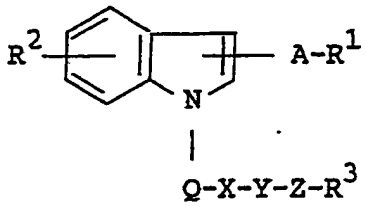
NMR ($CDCl_3$, δ) : 2.06 (2H, m), 2.46 (2H, t, J=7.5Hz), 2.77 (2H, t, J=7.5Hz), 3.43 (3H, s), 5.22 (2H, s), 7.14 (1H, s), 7.3-7.5 (2H, m), 7.61 (1H, d, J=7.5Hz), 7.7-8.0 (6H, m), 8.26 (2H, d, J=8Hz), 8.42 (1H, d, J=7.5Hz)

Example 10

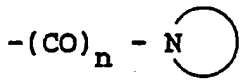
Chloromethyl methyl ether (0.17 ml) was added to a mixture of 4-[1-[4-(4'-benzyloxycarbonyl)biphenylcarbonyl]indol-3-yl]butyric acid (0.55 g) and potassium carbonate (0.21 g) in dimethylformamide (10 ml). The mixture was stirred at room temperature for 5 hours and partitioned between ethyl acetate and water. The organic layer was washed with water, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (40 g) using a mixture of n-hexane and ethyl acetate (5:1) as an eluent.

CLAIMS

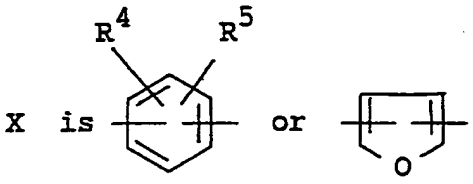
1. A compound of the formula :



wherein R^1 is carboxy or protected carboxy,
R^2 is hydrogen, lower alkyl or halogen,
R^3 is aryl or ar(lower)alkyl, each of which may have suitable substituent(s), or a group of the formula :



in which -N⌒ is heterocyclic group containing nitrogen atom, and
n is 0 or 1,
A is lower alkylene which may be substituted by oxo or lower alkenylene,
Q is carbonyl, sulfonyl or lower alkylene,



in which R^4 is hydrogen or lower alkyl, and
R^5 is hydrogen, lower alkyl or $Y-Z-R^3$,

Y is bond or lower alkylene,
Z is bond, lower alkylene, lower alkenylene,

-O-, -S- or -N- ,
in which R^6 is lower alkyl, ar(lower)alkyl which may have suitable substituent(s) or amino protective group; or
$X-Y-Z-R^3$ is 6H-dibenzo[b,d]pyranyl which may have suitable substituent(s),
and pharmaceutically acceptable salts thereof.

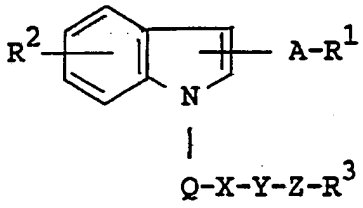
2. A compound of claim 1, wherein
R^1 is carboxy or esterified carboxy,
R^3 is aryl which may be substituted by one to three substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, halogen and lower alkylcarbamoyl, ar(lower)alkyl which may be substituted by one to three substituent(s) selected from lower alkyl, halogen, cyano, carboxy, esterified carboxy, amidated carboxy and oxo, and
R^6 is lower alkyl, ar(lower)alkyl which may be substituted by lower alkyl..

3. A compound of claim 2, wherein
R^1 is carboxy, lower alkoxycarbonyl or mono- or di- or triphenyl(lower)alkoxycarbonyl,
R^3 is phenyl substituted by one to three substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, halogen and lower alkylcarbamoyl, mono- or di- or triphenyl(lower)alkyl which may be substituted by one to three substituents

selected from lower alkyl, halogen, cyano, carboxy, mono- or di- or tri phenyl(lower)alkoxycarbonyl, mono- or di(lower)alkylcarbamoyl, phenylcarbamoyl, lower alkylphenylcarbamoyl and oxo

R^6 is lower alkyl, mono- or di- or triphenyl(lower)-alkyl which may be substituted by lower alkyl.

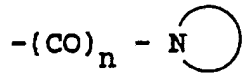
4. A process for preparing a compound of the formula :



wherein R^1 is carboxy or protected carboxy,

R^2 is hydrogen, lower alkyl or halogen,

R^3 is aryl or ar(lower)alkyl, each of which may have suitable substituent(s), or a group of the formula :

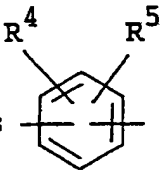
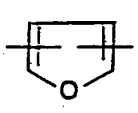


in which  is heterocyclic group containing nitrogen atom, and

n is 0 or 1,

A is lower alkylene which may be substituted by oxo or lower alkenylene,

Q is carbonyl, sulfonyl or lower alkylene,

X is  or 

in which R^4 is hydrogen or lower alkyl, and

R^5 is hydrogen, lower alkyl or $Y\text{-}Z\text{-}R^3$,

Y is bond or lower alkylene,

Z is bond, lower alkylene, lower alkenylene, $-O-$, $-S-$ or $-\overset{R^6}{\underset{|}{N}}-$,

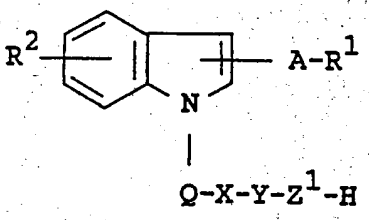
in which R^6 is lower alkyl, ar(lower)alkyl which may have suitable substituent(s) or amino protective group; or

$X\text{-}Y\text{-}Z\text{-}R^3$ is 6H-dibenzo[b,d]pyranyl which may have suitable substituents(s),

or a salt thereof,

which comprises,

(1) reacting a compound of the formula :



wherein R^1, R^2, A, Q, X, and Y are each as defined above, and

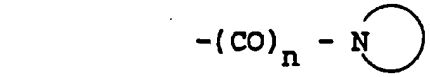
Z^1 is $-O-$, $-S-$ or $-\overset{R_a^6}{\underset{|}{N}}-$

in which R_a^6 is lower alkyl or amino protective group,

or a salt thereof, with a compound of the formula :

$$W^1\text{-}R_a^3$$

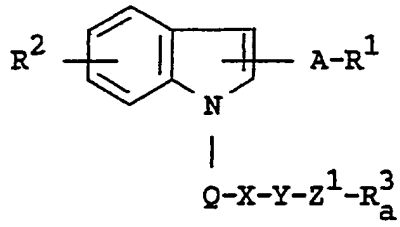
wherein R_a^3 is ar(lower)alkyl which may have suitable substituent(s) or a group of the formula :



in which  and n are each as defined above, and

W^1 is acid residue,

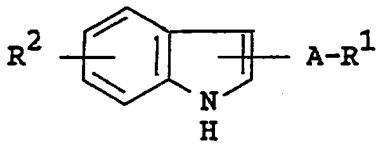
or a salt thereof, to give a compound of the formula:



wherein R^1, R^2, R_a^3, A, Q, X, Y and Z^1 are each as defined above,

or a salt thereof, or

(2) reacting a compound of the formula :



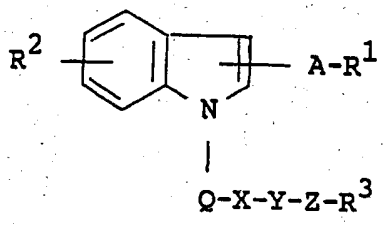
wherein R^1, R^2 and A are each as defined above,

or a salt thereof, with a compound of the formula :

$$W^2\text{-}Q\text{-}X\text{-}Y\text{-}Z\text{-}R^3$$

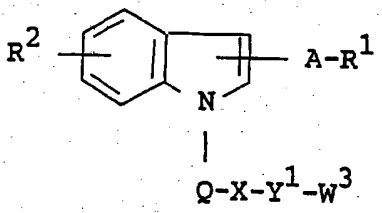
wherein R^1, R^3, Q, X, Y, Z and A are each as defined above, and

W^2 is acid residue,
or a salt thereof, to give a compound of the formula:



wherein R^1, R^2, R^3, A, Q, X, Y and Z are each as defined above,
or a salt thereof, or

(3) reacting a compound of the formula :



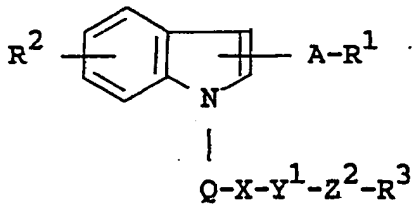
wherein R^1, R^2, A, Q and X are each as defined above,
W^3 is acid residue, and
Y^1 is lower alkylene,
or a salt thereof, with a compound of the formula :

$$H\text{-}Z^2\text{-}R^3$$

wherein R^3 is as defined above, and

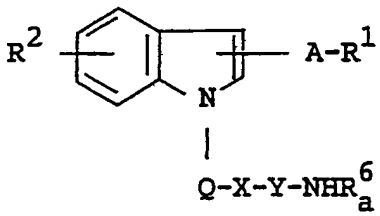
Z^2 is -O- or 

in which R^6 is as defined above,
or a salt thereof, to give a compound of the formula:



wherein R^1, R^2, R^3, A, Q, X, Y^1 and Z^2 are each as defined above,
or a salt thereof, or

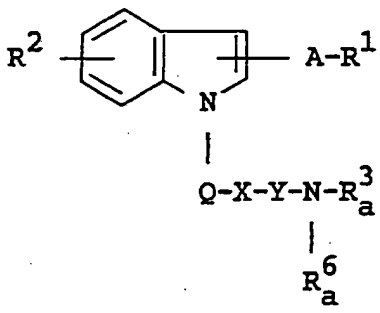
(4) reacting a compound of the formula :



wherein R^1, R^2, R_a^6, A, Q, X and Y are each as defined above,
or a salt thereof, with a compound of the formula :

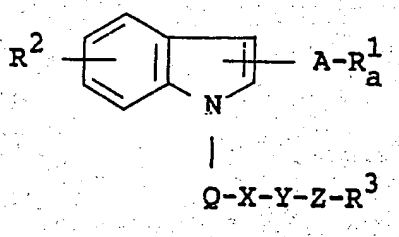
$$W^1 - R_a^3$$

wherein R_a^3 and W^1 are each as defined above,
or a salt thereof, to give a compound of the formula:

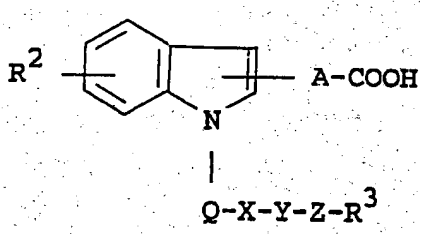


wherein R^1, R^2, R^3_a, R^6_a, A, Q, X and Y are each as defined above,
or a salt thereof, or

(5) subjecting a compound of the formula :

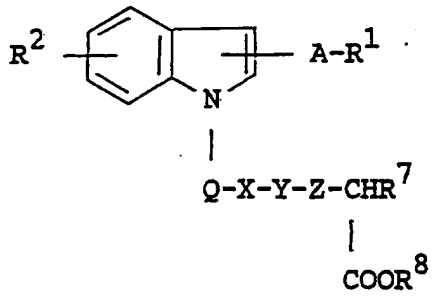


wherein R^2, R^3, A, Q, X, Y and Z are each as defined above, and
R^1_a is protected carboxy,
or a salt thereof, to elimination reaction of the carboxy protective group, to give a compound of the formula :

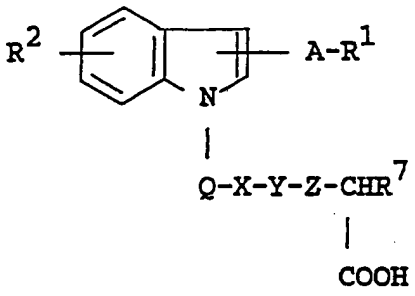


wherein R^2, R^3, A, Q, X, Y and Z are each as defined above,
or a salt thereof, or

(6) subjecting a compound of the formula :

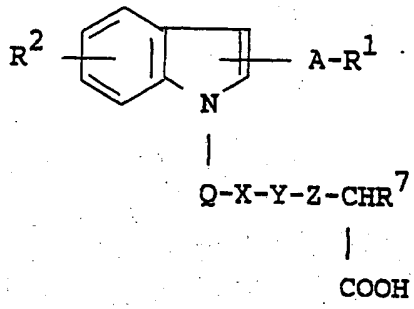


wherein R^1, R^2, A, Q, X, Y and Z are each as defined above,
R^7 is aryl which may have suitable substituent(s), and
R^8 is carboxy protective group,
or a salt thereof, to elimination reaction of the carboxy protective group, to give a compound of the formula :



wherein R^1, R^2, R^7, A, Q, X, Y and Z are each as defined above,
or a salt thereof, or

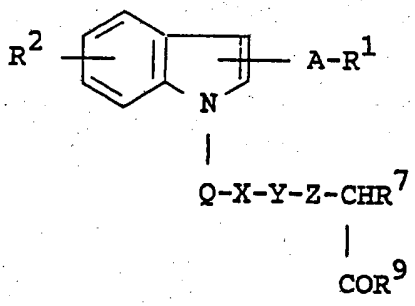
(7) reacting a compound of the formula :



wherein R^1, R^2, R^7, A, Q, X, Y and Z are each as defined above,
or its reactive derivative at the carboxy group or a salt thereof, with a compound of the formula :

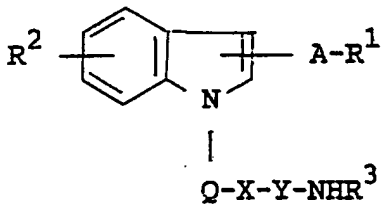
$$H\text{-}R^9$$

wherein R^9 is amino which may have suitable substituent(s),
or its reactive derivative at the amino group or a salt thereof, to give a compound of the formula:



wherein R^1, R^2, R^7, R^9, A, Q, X, Y and Z are each as defined above,
or a salt thereof, or

(8) reacting a compound of the formula :



wherein R^1, R^2, R^3, A, Q, X and Y are each as defined above,

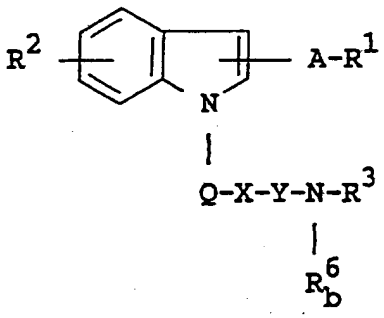
or a salt thereof, with a compound of the formula :

$$W^4\text{-}R_b^6$$

wherein R_b^6 is lower alkyl, ar(lower)alkyl which may have suitable substituent(s) or amino protective group, and

W^4 is acid residue,

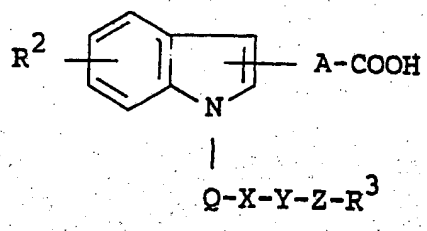
or a salt thereof, to give a compound of the formula:



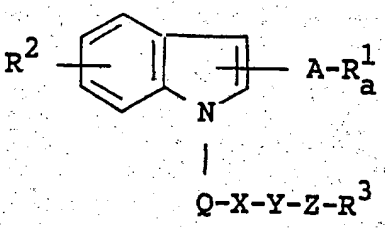
wherein R^1, R^2, R^3, R_b^6, A, Q, X and Y are each as defined above,

or a salt thereof, or

(9) subjecting a compound of the formula :



wherein R^2, R^3, A, Q, X, Y and Z are each as defined above,
or a salt thereof, to introduction of the carboxy protective group, to give a compound of the formula :



wherein R^1_a, R^2, R^3, A, Q, X, Y and Z are each as defined above,
or a salt thereof.

5. A pharmaceutical composition comprising a compound of claim 1 or pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

6. A method for treating or preventing testosteron 5α-reductase-mediated diseases, which comprises administering a compound of claim 1 or pharmaceutically acceptable salt thereof to human being or animals.

7. Use of a compound of claim 1 or pharmaceutically acceptable salt thereof as a medicament.

8. Use of compound of claim 1 or pharmaceutically acceptable salt thereof as a testosteron 5α-reductase inhibitor.

9. A process for preparing a pharmaceutical composition which comprises admixing a compound of claim 1 or pharmaceutically acceptable salt thereof with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP 92/00981

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 209/26 A 61 K 31/405 C 07 D 405/06

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 209/00 C 07 D 405/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
P,X	WO,A,9113060 (FUJISAWA PHARMACEUTICAL CO., LTD) 5 September 1991, see complete document	1,5,8

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
21-09-1992	21. 10. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Weinberg

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 92/00981

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 6 is directed is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has be en carried out and based on the alleged effects of the compound/composition

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. JP 9200981 SA 62818

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 15/10/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 9113060	05-09-91	AU-A- 7257991	18-09-91
		CN-A- 1054250	04-09-91